EFFECTS and a PCT application, PCT/US98/19429, entitled A DELIVERY OF ARGININE TO CAUSE BENEFICIAL EFFECTS are being prosecuted currently. All of these cases contain almost identical disclosures to the instant application with respect to the use of an hostile biophysical environment.

It is apparent from the Examiner's comment "...and in any case it is not clear what delivery mechanism which uses high ionic strength has to do with the claims..." that a clarification of the central aspect of the present invention may be useful as a preface to the Examiner's substantive rejections. The claims of the present invention are limited to a topical delivery vehicle for L-arginine. L-arginine hydrochloride provides a precursor to the molecule nitric oxide, NO. NO is the substance that relaxes the blood vessels, allowing for increased blood flow. The concentration of the L-arginine based compound, e.g., L-arginine hydrochloride, is preferably between 0.25 to 25% w/v. The underlying objective of the instant invention is to effectively deliver a nitric oxide releasing substance such as the highly charged molecule, L-arginine, into tissue. A novel principle advantageously employed by the Applicant to achieve this objective is to create a biophysically hostile environment in the delivery vehicle such that L-arginine would prefer to be in the tissue. Alternatively, L-arginine can be packaged in such a way that it is carried into tissue. Moreover, absorption of L-arginine into targeted tissue may be accomplished by neutralizing its charge by the derivitization of L-arginine to form a neutral salt. Specification page 3, lines 1-5.

The Applicant discloses various embodiments for the creation of an hostile biophysical environment. These include but are not limited to, a high ionic strength environment, high or low pH, and highly hydrophobic environments. Furthermore, the Applicant discloses various examples for packaging L-arginine so that it may be transported into targeted tissue. For example, the nitric oxide releasing substance, L-arginine may be packaged in liposomes or emulsions of collagen, collagen peptides, or other components of skin or basement membrane. Finally, an example of neutralization of the highly charged molecule, L-arginine, is the electronically neutral salt, arginine glutamate. Specification page 7, lines 5-9.

Choline chloride, sodium chloride and magnesium chloride are non-limiting examples of salts which provide a high ionic strength environment for the highly charged molecule, L-arginine. This high ionic strength environment is an example of an hostile biophysical environment for L-arginine. That is, the highly charged ionic strength provided by the salts to the L-arginine carrier is an unfavorable environment for the highly charged L-arginine which facilitates or promotes L-arginine migration out of the carrier and into a more hospitable, less charged environment such as human tissue. Specification page 7, lines 5-9.

An hostile biophysical environment for facilitating the absorption L-arginine into tissue may also be created by using other highly charged molecules such as polylysine, polyglutamine, polyaspartate or copolymers of such charged amino acids. Alternatively, an hostile biophysical environment may be created by placing

the highly charged L- arginine in an hydrophobic, oily environment such as in an oil-based cream containing little or no water. Specification page 7, lines 14-20.

In the instant invention, L-arginine hydrochloride is the preferred active nitric oxide releasing substance; because, it is the agent in nature itself, it is non-toxic, is highly soluble and it is inexpensive. However, other molecules could be used which are also precursors or donors of nitric oxide. These include the salt, arginine glutamate, the salt, arginine butyrate, and esters of arginine such as arginine ethyl ester or arginine butyl ester as well as other donors of nitric oxide. Specification page 6, lines 4-8.

Thus, the instant invention incorporates the novel and unobvious principle for delivering the nitric oxide releasing substance, L-arginine, via the creation of an hostile biophysical environment to produce the beneficial effects such as increasing local blood flow, promoting hair growth, healing of ulcers or restoration of normal erectile function in males suffering from erectile dysfunction. Specification page 4, lines 1-4. The base cream containing the nitric oxide releasing substance, choline chloride, sodium chloride and/or magnesium chloride serves as the topical delivery vehicle which produces these beneficial effects.

35 USC § 112 Second Paragraph Rejections

Once again claims 33-60 have been rejected under 35 USC §112 second paragraph as being indefinite for failing to particularly point out and distinctly

claim the subject matter which applicants regard as the invention. In making this rejection, the Examiner repeats the statement made in the 11/20/98 office action where he stated:

> It is not clear whether or not the materials in claim 39 and 47, etc. are meant to be used as alternatives or in combination since this is not stated in the claim.

Once again, the Applicant can only reiterate that the claims should be read literally. Claim 39 as written is dependent on claim 33. Claim 39 is very specific as to what the components are in the delivery vehicle. This claim is neither in the alternative, nor is it in combination. The words "or" and "combine" do not appear in this claim. Please note the term "wherein " is used in this dependent claim. Therefore, the basis of this rejection is not understood. Applicant respectfully requests withdrawal of this rejection.

Similarly, withdrawal of the rejection of claim 47 is also requested. Claim 47 as written is dependent on claim 42. As discussed *supra*, claim 47 is also very specific as to what delivery vehicle is being used to create the hostile biophysical environment. This claim is neither written in the alternative, nor does the applicant wish to imply the combination of materials. The claim should be interpreted literally. Therefore, withdrawal of this rejection is respectfully requested.

Applicant notes the Examiner's identical comments in both the 11/20/98 and 5/10/99 office actions in which he states:

> It is not clear if the concentration of ionic salt sufficient to create an ionic environment which causes a substance to migrate from the vehicle to the skin embraces zero concentrations of salt in that there is no reason why nitric oxide releasing substances cannot be absorbed by the skin even in the absence of salt.

In a previous response the Applicant argued:

> While it is true that nitric oxide substances can be absorbed by the skin in the absence of salt, the Applicant's use of a high ionic biophysical environment in the delivery vehicle increases the efficiency of the absorption of L-Arginine into tissue. As has been stated previously, one approach to effectuate absorption of a highly charged molecule such as L-arginine into tissue is to create a biophysically hostile environment in the delivery vehicle such that L-arginine would prefer to be in the tissue. Clearly, zero concentrations of salt would not work in a delivery mechanism that uses a high ionic strength to force the L-arginine out of the delivery vehicle and into tissue. Applicant, has found that the high salt hostile biophysical environment is the simplest and most efficient delivery mechanism for facilitating the absorption of L-arginine into tissue. For this reason, the claims of the instant invention teach the use of a high ionic strength environment. Therefore, Applicant respectfully requests that this rejection be withdrawn.

In the current office action, the Examiner revisits this rejection first made in office action mailed on 11/20/98. The Examiner states:

> With regard to the question of whether applicant's salt concentrations embrace 0 concentrations, applicant argues that 0 concentrations of salt would not work in a delivery mechanism that uses a high ionic strength to force the L-arginine out of the delivery vehicle into the tissue. However, the above rejection has nothing to do with enablement and in any case it is not clear what delivery mechanism which uses high ionic strength has to do with the claims. Applicants argue that the claims of the instant invention teach the use of a high ionic strength environment. However, no such limitation appears in the claims.

It should be noted that in making this 35 USC § 112 second paragraph indefiniteness rejection the Examiner's own language raised the issue of enablement by stating"...there is no reason why nitric oxide releasing substances cannot be absorbed by the skin even in the absence of salt." In order to comply with his 37 CFR § 1.111 obligation to "reply to every ground of objection and rejection in the prior office action," the Applicant addressed this rejection in the context in which it was raised. Therefore, the Applicant respectfully requests that the Examiner's objection regarding the format of the applicant's response be withdrawn.

In response to the Examiner's substantive rejection regarding the absence of the use of a high ionic strength environment as a limitation in the claims, Applicant respectfully traverses this rejection. As has been stated previously, the discovery to which these patent claims are limited is the novel and unobvious principle of employing an ionic solution of sufficient concentration to cause L-arginine to preferentially migrate from the topical delivery vehicle to the target tissue. In particular, as is stated in the instant application, the ionic strength of the salts necessary to create the hostile biophysical environment is high. See page 7, line 1. In fact, throughout the specification, the Applicant has repeatedly equated the terms "high ionic strength environment" and "biophyscially hostile environment" with the language of using a salt at a concentration sufficient to aid in tissue absorption. Specifically, page 5, lines 4-7 of the specification state

> ...choline chloride, sodium chloride and magnesium chloride provide a high ionic strength environment for the highly charged molecule, L-arginine. This high ionic strength environment is an example of a hostile biophysical environment for L-arginine. that is, the highly charged ionic strength is an unfavorable environment for the highly charged L-arginine making the L-arginine anxious to move to a more hospitable environment such as human tissue.

Thus, the claim language "a concentration of ionic salt sufficient to create an ionic environment which causes the substance to migrate from the vehicle to the skin where the substance is absorbed..." is clearly equated with a delivery mechanism which uses high ionic strength to those skilled in the chemical arts. Because support for equating this terminology is found throughout the specification, the Applicant is correct in asserting that the claims teach the use of a high ionic strength environment. Therefore, the claim language is not indefinite. The Applicant respectfully submits that claims 33-60 are allowable, and that the 35 USC §112 second paragraph rejection be withdrawn.

Finally, the Applicant wishes to draw the Examiner's attention to two related cases that contain identical claims as the instant invention with regard to the limitation "...a concentration of ionic salt sufficient to create an ionic environment..." U.S. Patent No. 5,895,658, issued on April. 20, 1999, concerns the topical delivery of L-Arginine to cause tissue warming. U.S. Patent No. 5,9222,332, issued on July 13, 1999, is directed to the topical delivery of arginine to overcome pain. In both of these issued cases, the specifications have identical language to the instant application with regard

to this issue. Specifically, under the heading "summary of the invention" the specification in the instant application as well as in these two issued patents states:

> In preferred embodiments, the delivery vehicle is a penetrating cream, the L-arginine is present as L-Arginine hydrochloride in a concentration sufficient to produce the desired effect and the agent which creates the hostile biophysical environment is sodium chloride at a concentration sufficient to aid in tissue absorption.

It should be noted that neither Examiner Howard nor Examiner Page considered claims drawn to this specification language indefinite when they used the language "...an ionic salt concentration sufficient to create an ionic strength environment which causes the substance to migrate from the vehicle..." Clearly, they recognized the Applicant's contention that delivery of the highly charged molecule, L-arginine, would require a high ionic strength environment. It is inherent in the teaching of the invention that the limitation regarding a concentration of an ionic salt sufficient to cause the highly charged L-arginine to wish to migrate from delivery vehicle is equivalent to the use of a high ionic strength environment. The applicant respectfully submits that in making his rejection, the Examiner has relied on an unique standard which is known to neither the applicant, nor the two other Examiner's who have reviewed the identical subject matter. For the forgoing reasons, Applicant respectfully submits that claims 33-60 are allowable in that they particularly point out and distinctly claim the subject

matter which Applicant regards as the invention. Applicant respectfully requests reconsideration, and that the §112 second paragraph be withdrawn.

35 USC §112 First Paragraph Rejections

Claims 35-38,44 and 53-55 have been rejected under 35 USC §112 first paragraph, as based on a disclosure which is not enabling. The Examiner states that the instant application "contains subject matter which was not described in the specification in such a way at to reasonably convey to one skilled in the relevant art that the inventor at the time the application was filed, had possession of the claimed invention." In making this rejection the Examiner States:

> There is nothing in the specification which discloses a combination of a hydrophobic delivery vehicle and an ionic salt. Note in this regard page 7 of the specification discloses that alternatively a hostile biophysical environment may be created by placing the highly charged L-arginine in an hydrophobic, oily environment such as in an oil-based cream containing little or no water. It is therefore clear that use of the hydrophobic vehicle is an alternative to the salt containing vehicles. Any claims reciting the limitation containing the hydrophobic delivery vehicle in combination with an ionic salt therefore lack support in the specification as filed and such limitation is new matter. Furthermore, salts in general are not soluble in hydrophobic delivery vehicles and it is not clear how the method of for instance claim 35 could be conducted which is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure.

In contrast to the Examiner's assertion that the instant invention as claimed is not enabling, the Applicant respectfully points out that the specification repeatedly discloses the use of an hostile biophysical environment for L-arginine created by a

high salt concentration and a delivery vehicle which is a penetrating base cream. Specifically on page 3 of the Applicant's disclosure under Summary of the Invention, it states: "In one embodiment of the invention, a penetrating cream containing L-arginine at an effective concentration and a salt, such as sodium chloride, at a concentration sufficient to create a hostile biophysical environment for the L-arginine in the cream is applied nightly to the scalp..."
Furthermore, on page 4 of the specification under Detailed Description of the Invention, the specification again discloses the combination of the hydrophobic delivery vehicle and the ionic salt where it states:
"The preferred embodiment consists of a base cream with the properties of excellent absorption into the skin which also includes L-arginine hydrochloride...The components of the base cream may be those commonly found in hand creams, such as water, mineral oil, glyceryl sterate..." Clearly, some of the ingredients of the base cream are hydrophobic. It is well known in the chemical arts that salts can be coupled with hydrophobic creams. In fact, topical delivery of the L-arginine salt would not be possible without the base cream delivery vehicle as taught in the instant invention. Thus, the claims as submitted are enabling and have support in the specification. Therefore, withdrawal of this rejection is respectfully requested.

Applicant respectfully acknowledges the Examiner's consideration of the arguments presented in the amendment to the office action mailed 11/20/98. In his

5/10/99 office action the Examiner elaborated upon the enablement rejection by stating:

> With regard to the issue of enablement, applicant argues that page 3 of the specification discloses that a salt may be used in the form of a cream. It is clear that the use of a salt is enabled, however there is nothing in this passage that indicates combination with a hydrophobic delivery vehicle. Applicant argues that a base cream is disclosed in which some of the ingredients are hydrophobic. While it may be true that some of the materials are inherently hydrophobic, it is not clear that a cream which is hydrophobic is disclosed in that hydrophilic materials such as water are also disclosed. Furthermore the term "delivery vehicle broader than the term "cream" and furthermore the disclosure of a single hydrophobic material cannot be sad to enable the disclosure of hydrophobic delivery vehicles.

Applicant notes the Examiner rejection and respectfully traverses. The Applicant wishes to draw the Examiner's attention to two related cases that contain identical claims as the instant invention with regard to the limitation of coupling an ionic salt with an hydrophobic delivery vehicle to create the hostile biophysical environment for the release of L-Arginine. U.S. Patent No. 5,895,658, issued on April. 20, 1999, concerns the topical delivery of L-Arginine to cause tissue warming. U.S. Patent No. 5,9222,332, issued on July 13, 1999, is directed to the topical delivery of arginine to overcome pain. In both of these issued cases, the specifications have identical language to the instant application appearing under the heading "other means for effecting or improving absorption" at page 6, lines 14-19, and page 7, lines 1-22. It should be noted that neither Examiner Howard nor Examiner Page considered these specifications non-enabling. Furthermore, as was

noted previously, identical claim language was used, and neither of these examiners objected to the use of the term vehicle instead of "cream"; because, the former was considered too broad. Finally, there is yet another related pending case, U.S. Ser. No. 08/936,189, directed to the topical and oral delivery of Arginine to cause beneficial effects. Yet again, the language in the specification is identical to the language used in the instant application with respect to other embodiments for the creation of an hostile biophysical environment for the delivery of L-arginine into the target tissue. During the prosecution of this case, Examiner Faulkner never issued a § 112 first paragraph enablement rejection due to the applicant's claiming the combination of an ionic salt with an hydrophobic delivery vehicle. As has been stated previously, it is well known in the chemical arts that an ionic salt may be coupled with an hydrophobic environment such as an oil-based cream. The applicant respectfully submits that in making his rejection, the Examiner has relied on an unique standard which is known to neither the applicant, nor the three other Examiner's who have reviewed the identical subject matter. Therefore, Applicant respectfully submits that claims 35-38, 44, and 53-55 are allowable and requests that the 35 USC §112 first paragraph rejection of these claims be withdrawn.

35 USC § 102 Rejections

It is particularly apparent from the prior art cited by the Examiner that it is known that the introduction of nitric oxide in the body produces desirable effects, including penile erection, hair growth muscle relaxation and increased circulation of blood flow to the surrounding tissue. Indeed, the art cited by the Examiner discloses these exact effects. It is also clear from the art cited by the Examiner that L-arginine, L-arginine salts and L-arginine derivatives are known to effectively release nitric oxide.

Specifically, the Examiner cites Weuffen et al. as disclosing "a process in which an arginine containing substance in combination with various salts are applied to the scalp to promote hair growth." However, careful reading of this reference shows that the invention uses

> preparations based on alkali metal, alkaline earth metal and/or ammonium salts of thiocyanic acid and are characterized in that they contain as a further constituent, at least one component or mixtures selected from estrogens, sulfur, sulfide ions, vasodilators, skin-active vitamins, inorganic selenium compounds, amino acids and carboxylic acids physiologically occurring in the skin...See Column 3, lines 14-22 in Patent No. 5, 629,002.

Nowhere in this reference is the topical use of L-arginine discussed in conjunction with the promotion of hair growth. Instead, this reference discloses the use of thiocyanates as the active ingredient. More importantly, this reference does not disclose the use of an hostile biophysical environment as a means of facilitating the delivery of L-arginine to the tissue. It is this novel functionality of the hostile

biophysical environment NO delivery system taught by the instant invention that is neither explicitly or implicitly taught or suggested in the prior art.

As the examiner knows, a reference will only anticipate an invention under 35 USC § 102(b) if each and every element is identically disclosed by the single cited reference. *Corning Glass Works v. Sumitomo Electric,* 9 U.S.P.Q. 2d (BNA) 1962,1965 (Fed. Cir. 1989). In other words, the absence of a claimed element regardless of its insubstantial or obvious nature shall defeat a novelty rejection. *Connel v. Sears Roebuck & Co.,* 220 U.S.P.Q. (BNA) 193,198 (Fed. Cir. 1983). Finally, the courts have determined "Invalidity based on lack of novelty (often called anticipation) requires the same invention, including each and every element and limitation of the claims, was known or used by others before it was invented by the patentee." *Scripps Clinic & Research Found. v. Genetech, Inc.* 927 F 2d 1565, 1576, 18 U.S.P.Q. 2d 1001, 101 (Fed. Cir. 1991). Therefore, because Weuffen reference does not have the limitation of an hostile biophysical environment, the instant invention is not anticipated by the Weuffen reference. Thus, the applicant respectfully requests withdrawal of this rejection.

Claims 33-34 and 39 are rejected under 35 USC § 102(a) as being anticipated by Hechtman. In making this rejection the Examiner states: "Hechtman discloses a topical treatment in which L-arginine is applied to an area being treated whereby nitric oxide is released." As discussed *supra,* Applicant acknowledges that the prior art discloses the beneficial effects of NO. Applicant is not claiming these actions.

Instead, the claims of Applicant's invention disclose a novel L-arginine delivery system for the NO precursor. Nowhere in this Hechtman reference is the creation of an hostile biophysical environment for the delivery of L-arginine disclosed. Specifically, with respect to the Examiner's comment regarding the electrolyte solution disclosed in claim 6 of the patent, Applicant notes that this electrolyte solution is not limited to an ionic strength which is high enough to create an hostile biophysical environment. Because the cited reference fails to disclose all of the material elements in a claim, Hechtman does not anticipate the instant invention. Accordingly, Applicants respectfully request that this § 102(b) rejection be withdrawn upon reconsideration. It is believed that the basis upon which the Examiner made the § 102(b) rejections has been removed by this amendment.

35 USC 103 REJECTIONS

Claims 33-60 have been rejected under 35 USC 103(a) as being unpatentable over Garfield et al in view of Hechtman, Altadonna, Cook et al., Saavedra et al. In making this rejection the Examiner states:

> Garfield et al. disclose a process for healing wounds, treating impotence and restoring hair growth by topical application of an active ingredient. Note column 6 line 40 - column 5 line 50. The active ingredient is a nitric oxide donor at column 6 lines 4-22. Excipients such as salt solutions for influencing osmotic pressure and vegetable oils may be added and the composition may be in the form of transdermal patches at column 8 line 65 - column 9 line 5. Since the application of nitric oxide increases blood flow, increasing blood flow would be inherent in the reference.

The Applicant respectfully traverses. While the Examiner cites Garfield as disclosing a process for healing wounds, treating impotence and restoring hair growth by the topical application of an active ingredient, there is no mention of an hostile biophysical environment used in combination with a nitric oxide precursor such as L-Arginine. In fact, the examiner acknowledges that this reference does not teach the novel and unobvious combination of using an ionic solution of sufficient concentration so as to create an hostile biophysical environment to cause the migration of L-arginine into target tissue when he states:

> Garfield et al. do not disclose the use of arginine or the use of ionic salts to increase penetration or the use of arginine glutamate or application of nitric oxide releasing substances to the penis.

Therefore, this reference alone or in combination with the other cited art does not render the instant invention obvious.

The Examiner continues his §103 rejection by stating:

> Hechtman discloses that arginine may be applied topically to enhance nitric oxide production in tissues requiring such (Abstract, column 9 lines 56-61) and is taught to be particularly safe in comparison to other nitric oxide precursor substances (column 2 lines 9-18).
>
> Cook et al. disclose that arginine glutamate functions to release nitric oxide in tissues requiring such (column 4 lines 17-30).
>
> Altadonna (USP 5,853,768) discloses that iodide salts increase penetration of topically applied medicaments. Note the abstract.
>
> Saavedra et al. disclose treating impotence by placing a nitric oxide generating substance inside a condom and then placing a condom on the penis at column 10, lines 20-35.

Applicant respectfully traverses this rejection. The Examiner cites Saavedra et al. as disclosing a process for treating impotence in which a nitric oxide releasing substance is incorporated into a condom, the composition being in the form of liposomes or a patch which is applied topically. It also discloses that saline may be used. However, Saavedra does not disclose the creation of an hostile biophysical environment. In fact, the use of the biophysically hostile environment is what drives the nitric oxide precursor, L-arginine from the delivery vehicle into the surrounding skin. The mere use of saline will not potentiate the delivery of L-arginine. In fact, if L-arginine is mixed with a topical cream, nothing will happen.

The Examiner also cites Cooke et al. as disclosing that arginine glutamate is a nitric oxide precursor that causes nitric oxide to be released into tissue. Applicant reiterates, he is not claiming the beneficial effects of arginine as a nitric oxide precursor; instead, Applicant's invention is directed to a novel and unobvious method for the facilitation of the delivery of L-arginine into target tissue through the creation of an hostile biophysical environment.

Finally, the Examiner cites Altadonna as disclosing that iodide salts potentiate the penetration of topically applied medicaments. However, careful review of this references reveals the iodide salts are acting as a disinfectant. They are not of a sufficient concentration to cause the migration of L-arginine from the topical delivery vehicle. Moreover, the topical preparation in Altadonna contains menthol and camphor, and these ingredients are acting in conjunction with oleyl

ether phosphate for the relief of pain. In fact, the pain relief mechanism disclosed in this reference teaches away from the instant invention. Pain relief in the Altadonna reference is achieved by the "novel composition of complex oleic ether phosphate...used in combination in Oleth 10, camphor and other active ingredients including lanolin, methyl glucose, iodine containing substances..." No mention is made of the use of an hostile biophysical environment to induce L-arginine to preferentially migrate from the vehicle to the skin to produce the desired effects.

The *Rijckaert* court has held, " in rejecting claims under 36 USC § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness." *In re Rijckaert,* 9 F.3d 1531,1532, 28 U.S.P.Q. 2d (BNA) (Fed. Cir. 1993). Only if the examiner meets this burden does the burden then shift to the applicant to come forth with evidence or argument to rebut the obviousness rejection. "If the examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned." *Id.* Applicant respectfully suggest that the Examiner has failed to meet establish a *prima facie* case of obviousness for the reasons discussed *infra.*

In order to sustain an obviousness rejection under 35 USC § 103(a), the Examiner must establish that there is some teaching, suggestion or motivation either implicitly or explicitly to combine or modify the references cited, and the motivation to do so must be found in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See MPEP § 2143.01. While in his rejection the Examiner asserts:

> It would have been obvious to a practitioner having an ordinary skill in the art at the time of the invention to use the arginine glutamate of Cook et al. in the process of Garfield et al. motivated by Cook et al's disclosure that arginine glutamate functions to release nitric oxide in tissue by the consequent expectation that arginine glutamate of Cook et al would function as well as the nitric oxide releasing materials of Garfield et al. in the process of Garfield et al. absent any showing of surprising or unexpected results.
>
> It would have been obvious to a practitioner having an ordinary skill in the art at the time of the invention to add salts to the composition of Garfield et al. as taught by Altadonna in order to obtain the benefit of increased penetration absent any showing of surprising or unexpected results.
>
> It would have been obvious to a practitioner having an ordinary skill in the art at the time of the invention to apply the composition of Garfield et al. as modified by the secondary references to the penis as taught by Saavedra et al. motivated by the need to treat impotence as taught by Garfield et al. by Saavedra's disclosure that this could be done by topical application to the penis absent any showing of surprising or unexpected results.
>
> It would have been obvious to a practitioner having an ordinary skill in the art at the time of the invention to apply the composition of Garfield et al. as modified by the secondary references to the penis as taught by Saavedra et al. motivated by the need to treat impotence as taught by Garfield et al. by Saavedra's disclosure that this could be done by topical application to the penis absent any showing of surprising or unexpected results.

he fails to support these statements. To the contrary, neither Garfield, Saavedra, Altadonna, nor any of the other cited documents suggest providing an hostile biophysical environment to facilitate the migration of L-arginine from the delivery vehicle to the target tissue. Instead this novel and unobvious delivery mechanism is only taught in the instant invention. In fact, the combination the of the cited documents teaches away from the instant invention. The combination of these

references may result in the release of the nitric oxide precursor, L-arginine, to cause various beneficial effects. However, it is in no way possible to derive therefrom a method for the delivery of L-arginine via the creation an hostile biophysical environment. As has been stated previously, none of these documents are based on the discovery that including a carrier with excess salt induces L-arginine to preferentially migrate from the delivery vehicle to produce the beneficial effects attributed to nitric oxide.

Therefore, Applicant contends that the Garfield, Hechtman, Altadonna, Cooke and Saavedra references are not properly combinable as they teach away from the applicant's invention. Under *In re Mercer,* the court has held if references teach away from the combination, the references are not properly combinable. *In re Mercer,* 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975). Furthermore, in order to properly combine references there must be some "suggestion of desirability" in the combination. *In re Nozik, Tatter, and Obbenauf,* 178 U.S.P.Q. 43, 45 (C.C.P.A. 1973). Neither meet this test as there is no suggestion in these references to create a method advantageously configured so as to

In addition to the fact that the cited references teach away from the instant invention, the Examiner's obviousness rejection may also be traversed because he has failed to support the conclusion that the combination of the limitations claimed by the applicant is suggested in the prior art teachings as required by MPEP § 2143.01. Moreover, the courts have held that the teaching or suggestion to make

the claimed invention must be found in the prior art, and not in the applicant's disclosure. *In re Veck,* F.2d 488,20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). In fact there is no suggestion in the cited references either implicitly or explicitly to use an hostile biophysical environment to encourage L-arginine to migrate from a delivery vehicle to the target tissue. The combination of these elements arises only in the Applicant's disclosure. Applicant respectfully suggests the Examiner has improperly relied on hindsight in suggesting that the combination of the references teaches or suggests the applicant's invention. Applicant respectfully requests, if the claims are again rejected upon any combination of references, that the Examiner include an explanation, in accordance with MPEP § 706.02 *Ex parte Clapp,* 278 U.S. P.Q. 972 (P.O.B.A. 1985), and *Ex parte Lkevengood,* supra, a "factual basis to support his conclusion that it would have been obvious" to make the combination.

Additionally, even if the claimed invention is within the capabilities of one of ordinary skill in the art as asserted by the Examiner, this alone is insufficient to render the invention obvious. See MPEP § 2143.01. The fact that those skilled in the art have not implemented the use of an hostile biophysical environment to drive L-arginine into tissue, indicates the present invention is not obvious.

In summary, there is nothing in Garfield, Hechtman, Altadonna, Cooke, or Saavedra which would have given one skilled in the art, at the time of the invention was made, any incentive to combine the teachings thereof to achieve a method for the delivery of L-arginine into tissue which incorporates an hostile biophysical

environment. Non of the cited references teach any of the embodiments for an hostile biophysical environment claimed in the instant invention, Namely, high ionic strength, high or low pH, or a highly hydrophobic environment. Therefore, in light of the above discussion, Applicant respectfully requests reconsideration and withdrawal of the 35 USC § 103(a) rejection. Accordingly, Applicant believes that the claims as amended are now in condition for allowance.

Applicant notes the Examiner's rejections of claims 33-34,38,39,51-54,56,59, and 60 as being obvious over Weuffen et al. In making this rejection, the Examiner used the identical arguments as were used in his §102 rejection of these claims. Furthermore, Applicant takes note of Examiner's §103 rejection of claims 33-34 and 39 wherein he states "or, in the alternative, under 35 USC 103(a) as being obvious over Hechtman (USP 5,595,753).

Applicant acknowledges the Examiner's consideration of the previously submitted arguments and notes the Examiner's further elaboration of his rejections based on the Hechman and Weuffen references in which he states:

> with regard to the rejection relying on Weuffen et al., applicants argue that there is nothing in the reference discussed in conjunction with promotion of hair growth. However column 14 lines 58-60 specifically discloses that the preparations were applied as a hair pack. Furthermore, column 14 lines 61-65 specifically refers to hair growth effect. While the effect is ascribed to thiocyanate, the composition specifically is taught to include arginine at column 14, lines 45-50 which is a nitric oxide releasing substance. With regard to applicant's argument regarding "an hostile biophysical environment," the instant claims do not require this and in any case such would appear to be inherent in the reference in that salts are present.

As the Examiner has acknowledged, the promotion of hair growth in the Weuffen reference is attributed to thiocyanate. Applicant wishes to direct the Examiner's attention once again to the fact that the Applicant is **not** claiming that L-arginine will promote hair growth. Instead, the salient principle underlying the Applicant's invention is a novel and unobvious method of delivering L-arginine to target tissue to achieve the beneficial effect of promoting hair growth. The mere fact that the cited reference also mentions arginine and salt as ancillary ingredients to the topical preparation in no way implies that an hostile biophysical environment is inherently present. In fact, as has been stated previously, the concentration of salt must be high enough to create an hostile biophysical environment for the highly charged L-arginine. The cited reference does not teach the use of a high salt concentration. Therefore, this reference does not render the instant invention obvious.

Applicant notes the Examiner's elaborated § 103 rejection based on the Hechtman reference in which he states:

> With regard to Hechtman, again applicants argue that a hostile biophysical environment is not disclosed by the reference. Again however the claims do not require such and with regard to applicant's argument. The cited reference that patentees' electrolyte solution would not necessarily have a high ionic strength to create such an environment, this is applicant's burden to prove.

As was discussed previously with regard to the 35 USC § 112 second paragraph rejection, the claims in the applicant's invention do require the use of an hostile biophysical environment. Specifically, the language in the claims concerning the use of an ionic solution of sufficient concentration is analogous to the term hostile biophysical environment. Therefore, because the instant invention is directed to the discovery of using an hostile biophysical environment to deliver L-arginine from a carrier into tissue, and Hechtman fails to disclose or imply such a method, the instant invention is not obvious in light of Hechtman.

As discussed *supra,* there is nothing in either Weuffen et al. or Hechtman et al, or their combination, which either teaches or suggests either implicitly or explicitly, the use of an hostile biophysical in the delivery vehicle for the facilitation of the delivery of L-arginine into tissue. Accordingly, Applicant submits that neither of these references renders the instant invention obvious. Applicant respectfully submits in light of the foregoing remarks, all of the claims are now in a condition for allowance. Applicant respectfully requests reconsideration.

Finally, while the Applicant has addressed the Examiner's substantive rejections, he wishes to wishes to point out to the Examiner that a procedural error with respect to some of the rejections has occurred. Specifically, a number of §103(a) rejections communicated in this third office action are identical to rejections cited by the Examiner in his first office action of March 3, 1998. The following rejections appeared in both office actions:

> Garfield et al. disclose a process for healing wounds, treating impotence and restoring hair growth by topical application of an active ingredient. Note column 6 line 40 - column 5 line 50. The active ingredient is a nitric oxide donor at column 6 lines 4-22. Excipients such as salt solutions for influencing osmotic pressure and vegetable oils may be added and the composition may be in the form of transdermal patches at column 8 line 65 - column 9 line 5. Since the application of nitric oxide increases blood flow, increasing blood flow would be inherent in the reference.
>
> Hechtman discloses that arginine may be applied topically to enhance nitric oxide production in tissues requiring such (Abstract, column 9 lines 56-61) and is taught to be particularly safe in comparison to other nitric oxide precursor substances (column 2 lines 9-18).
>
> Cook et al. disclose that arginine glutamate functions to release nitric oxide in tissues requiring such (column 4 lines 17-30).
>
> It would have been obvious to a practitioner having an ordinary skill in the art at the time of the invention to use the arginine glutamate of Cook et al. in the process of Garfield et al. motivated by Cook et al's disclosure that arginine glutamate functions to release nitric oxide in tissue by the consequent expectation that arginine glutamate of Cook et al would function as well as the nitric oxide releasing materials of Garfield et al. in the process of Garfield et al. absent any showing of surprising or unexpected results.

It should be noted that in his second office action, dated 11/20/98, the Examiner stated that all of these "previous rejections have been withdrawn. The withdrawal of the previous rejections based on the prior art is based on the assumption that applicants' claims do not embrace a non-zero quantity of salt." Given that Applicant acknowledged in his second response, dated 2/17/99, that "clearly, zero concentrations of salt would not work in a delivery mechanism that uses a high ionic strength to force the L-arginine out of the delivery vehicle and into tissue," Applicant does not understand why these rejections from the first office

action have been resurrected in the third office action. Applicant wishes to point out to the Examiner that there is a duty to expedite prosecution. This duty is reiterated in the commentary of the Patent Commissioner which states "The PTO will take steps to ensure that the processing of applications are being handled expeditiously." *Commentary of the Commissioner,* 60 Fed. Reg. No. 79 20, 205, April 25, 1995. In view of this duty to expedite the prosecution of patent applications, the Applicant requests that these rejections which were previously withdrawn, be withdrawn once again as the basis for withdrawal of these rejections has been satisfied by the Applicant.

Respectfully submitted,

LORUSSO & LOUD

Anthony M. Lorusso
Reg. No. 25, 059
LORUSSO & LOUD
440 Commercial Street
Boston, MA 02109
Tel.: (617) 227-0700
Fax.: (617) 723-4609

Dated August 6, 1999

Certification Under 37 CFR § 1.8

I hereby certify that this Amendment and Response to the Official Action dated 5/10/99 and any document referred to therein as being attached or enclosed is being deposited with the United States Postal Service on August 6, 1999 as postage pre-paid first class mail in an envelope addressed to : Assistant Commissioner for Patents, Washington, D.C. 20231.

Andrea Korson

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